REMARKS

The foregoing cancels claims 1-4 and 7-9, without prejudice or disclaimer.

Upon entry of these amendments, claims 5 and 6 will be pending. Applicants respectfully request reconsideration of these claims in view of the following remarks.

Specification

The Examiner objected to the title of the application. Applicants have amended the title.

The Examiner objected to the specification because it is inconsistent with the Application Data Sheet with respect to related applications. With this amendment, the specification has been amended to update the information on related applications.

The Examiner objected to Figures 11-1 to 11-4 under 1.58(a) and 1.83, as allegedly a duplicate of the sequence listing. Applicants respectfully respond that cancellation is not required. Figures 11-1 through 11-4 show a nucleotide sequence that is 5393 nucleotides in length and starts with the sequence "CTGTGTCCCG...". SEQ ID NO:1 lists a nucleotide sequence that is 5470 nucleotides in length and starts with the sequence "TATAGGGCGA..." Therefore, Figures 11-1 to 11-4 contain different sequence information than is contained in the sequence listing and hence do not exactly "duplicate" the information in the sequence listing. Therefore, cancellation of Figures 11-1 to 11-4 is not required.

Double Patenting Rejection

Claims 1-6 were rejected under the doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 1-9 of U.S. Patent 5,851,999.

Applicants request that the Examiner hold this rejection in abeyance until the subject matter of claims 5-6 is otherwise deemed allowable. At that time, Applicants intend to submit a terminal disclaimer, which will obviate the rejection.

Rejection under 35 U.S.C. §103

Claims 1-6 were rejected as being obvious over Lemischka (U.S. 5,185,438), Matthews *et al.* ("Matthews") and Termen *et al.* ("Termen") in view of Ulrich *et al.* ("Ulrich") and Ueno *et al.* (including "Ueno-1" and "Ueno-2"). Claims 1-4 have been cancelled, rendering the rejection moot with respect to those claims.

The Office alleges that the three primary references teach that Flk-1 is a VEGF receptor belonging to the class of type III tyrosine kinase receptors, with strong homology to the c-Kit family of receptors, and that Flk-1 DNA can be inserted into vectors. In particular, it states that Lemischka discloses soluble forms of the Flk-1 receptor and vectors containing the DNA, that Matthews discloses a recombinant vector comprising cDNA encoding Flk-1, and that Terman discloses cDNA encoding a receptor called KDR, a receptor of VEGF and the human homologue of Flk-1. The Examiner acknowledges, however, that none of these references teach or suggest constructing a recombinant vector encoding a truncated form of Flk-1 as recited in the rejected claims.

The Office further alleges that Ullrich and the two Ueno publications disclose three different receptor proteins that are truncated by the deletion of all or a portion of the intracellular domain. It then concludes that it would have been obvious for a person skilled in the art at the time of invention to modify the nucleic acids and recombinant vectors of the Lemischka, Matthews or Terman to delete all or a portion of the sequence encoding the intracellular domain, as taught by Ullrich or the Ueno publications.

As motivation to combine the teachings of the six cited references, the Office cites Terman's suggestion that Flk-1 is a homolog of the murine KDR receptor and that it would be "desirable to investigate the dimeric combinations in which the receptor occurs, and the relationship of such to the physiological responses known to occur in response to the ligand, VEGF . . . ." The Office also cites teachings from Ullrich and Ueno as providing motivation to combine the references.

Applicants respectfully traverse the rejection.

To form a proper basis for a rejection under 35 U.S.C. § 103, prior art must supply both a motivation for making the claimed invention and a reasonable expectation of success for obtaining the claimed invention. In the present case, the cited references would not motivate one skilled in the art to make a truncated Flk-1 receptor having a functional Flk-1 extracellular and transmembrane domain, and which inhibits the cellular effects of VEGF binding. Also, there was no expectation for success in making such truncated receptors at the time of invention.

Lemischka, Matthews and Terman purportedly describe cDNA sequences for wild-type Flk-1. None of these primary references, however, suggest the generation of truncated Flk-1 that has a functional extracellular and transmembrane domain. Moreover, none of these references suggests that expression of Flk-1 is specifically associated with endothelial cells or that a truncated Flk-1 could inhibit the cellular effects of VEGF binding.

Ullrich, Ueno 1 and Ueno 2 do not remedy the defects of the primary references. They describe various truncated receptor tyrosine kinases and show that early events in receptor tyrosine kinase signal transduction can be affected by such kinases in an artificial overexpression system. They do not, however, teach or suggest that truncated mutants would inhibit the biological response of endogenous receptors in a highly specific manner. Additionally, none of the references suggest that the truncated proteins are related to the Flk-1 receptor protein or that a truncated Flk-1 receptor protein would behave in a similar manner. Therefore, the references provide no reason for one skilled in the art to make truncated Flk-1 proteins of the present invention.

Indeed, it was entirely unexpected that truncated Flk-1 variants would have an inhibitory effect on the cellular response of VEGF and that polynucleotides encoding truncated Flk-1 variants would be useful for gene therapy of tumors by specifically inhibiting the growth of blood vessels *in vivo*.

Such results were unexpected because at least one other receptor, flt-1, was known to bind VEGF with high affinity. It also was known that flt-1 is expressed in endothelial cells of a

growing tumor.[1] Significantly, flt-1 has a 50-fold higher affinity for VEGF than Flk-1.[2] Consequently, the skilled artisan would not have expected that blocking the Flk-1 signaling pathway would shut down the cellular response to VEGF, resulting in suppression of angiogenesis and inhibition of tumor growth. Rather, one of ordinary skill in the art would have anticipated that the biological response to VEGF, such as the proliferation of blood vessels, would still be transduced through flt-1. For at least this reason, the ability of the claimed truncated Flk-1 receptor proteins to inhibit angiogenesis were unexpected.

Thus, without Applicants' disclosure of the favorable properties of truncated Flk-1 receptor proteins, one skilled in the art would not have been motivated to make them or had any reasonable expectation of success for using them in any practical way. It therefore appears that the Office has used hindsight to provide a motivation to combine the primary and secondary references. This is improper, as the law clearly requires that, for a rejection under 35 U.S.C. § 103, both the motivation and reasonable expectation for successfully making an invention must be found within the prior art, and not be gleaned from Applicants' disclosure.[3]

Accordingly, Applicants respectfully request withdrawal of the rejection.

Conclusion

Applicants believe that the present application is now in condition for allowance, and an early notice to that effect is earnestly solicited.

Should there be any questions regarding this submission, or should any issue remain, the Examiner is invited to contact the undersigned by telephone in order to advance prosecution.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment,

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[1] See, Plate *et al.*, 1992, Nature 359: 845-848; Plate *et al.*, 1993, Cancer research 53: 5822-5827. (Ref. A35)

[2] See, Waltenberger *et al.*, 1994, J. Biol. Chem. 269: 26988-26995.

[3] *In re Vaeck*, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991); *In re Dow Chemical Co.*, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988).

to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check or credit card payment form being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicants hereby petition for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

Date 10/12/07

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